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(54) METHOD FOR PREPARATION OF MODEL ANIMAL OF ARTHROPATHY

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a model animal of arthropathy such as degenerative joint disease.
SOLUTION: The tibial collaterial ligament, the anterior crucial ligament and the posterior crucial ligament of an essentially non-human mammal, especially rat are cut and the medial meniscus disc is cut off to induce the breakage of the joint and obtain a model animal free from the meniscus disk ligament.

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CLAIMS

[Claim(s)]
[Claim 1] the tibial collateral ligament, anterior cruciate ligament, and posterior cruciate ligament of a nonhuman mammal -- cutting -- further -- said -- the manufacturing method of the cell which constitutes the meniscus syndesmectomy model nonhuman mammal characterized by making joint destruction induce substantially by excising the inside knee meniscus of a leg, its joint, its joint organization, or its joint.
[Claim 2] The manufacturing method according to claim 1 whose nonhuman mammal is a rat.
[Claim 3] The manufacturing method of the cell which constitutes the meniscus syndesmectomy model nonhuman mammal containing the gene concerned characterized by medicating with a gene the nonhuman mammal obtained by the manufacturing method according to claim 1, its joint, its joint organization, or its joint.
[Claim 4] The manufacturing method of the cell which constitutes the nonhuman mammal which has the capacity which produces the gene product concerned characterized by medicating with a gene the nonhuman mammal obtained by the manufacturing method according to claim 1, its joint, its joint organization, or its joint.
[Claim 5] The manufacturing method according to claim 1 to 4 which is the animal a nonhuman mammal can imagine the drug effect or the gene function of a drug, a gene, or a gene product to be.
[Claim 6] The manufacturing method according to claim 3 or 4 whose gene is the ** sense DNA, ** antisense DNA, ** virus vector, or ** plasmid vector.
[Claim 7] The manufacturing method according to claim 3 or 4 whose gene is an articular disease specific fluctuation gene.
[Claim 8] How to solve the function of the gene concerned to which a function is characterized by prescribing an unknown gene for the patient, or its gene product to the nonhuman mammal obtained by the manufacturing

method according to claim 1.
[Claim 9] The approach according to claim 8 characterized by searching change of the cell which constitutes the nonhuman mammal concerned when not prescribing a medicine for the patient with the case where a gene with an unknown function is prescribed for the patient, its joint, a joint organization, or a joint.
[Claim 10] The approach according to claim 8 characterized by searching the function of the cell which constitutes the nonhuman mammal concerned when not prescribing a medicine for the patient with the case where a gene with an unknown function is prescribed for the patient, its joint, a joint organization, or a joint.
[Claim 11] The gene characterized by including the cell which constitutes the nonhuman mammal obtained by the manufacturing method according to claim 1, its joint, its joint organization, or a joint, or the kit for a functional break through of the gene product.
[Claim 12] The gene concerned characterized by including the cell which constitutes the nonhuman mammal containing the gene obtained by the manufacturing method according to claim 3, its joint, its joint organization, or a joint, or the kit for a functional break through of the gene product.
[Claim 13] The gene concerned characterized by including the cell which constitutes the nonhuman mammal which has the capacity which produces the gene product acquired by the manufacturing method according to claim 4, its joint, its joint organization, or its joint, or the kit for a functional break through of the gene product.
[Claim 14] The remedy which comes to contain the gene as which the function was solved using an approach or a kit according to claim 11 to 13 according to claim 8 to 10.
[Claim 15] The remedy which comes to contain the gene product of a gene with which the function was solved using an approach or a kit according to claim 11 to 13 according to claim 8 to 10.
[Claim 16] The remedy according to claim 14 or 15 which is articular disease accommodation medicine.
[Claim 17] The remedy according to claim 16 which is fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or prevention / therapy agent of rheumatoid arthritis.
[Claim 18] The screening approach of the articular disease accommodation medicine characterized by using the cell which constitutes the nonhuman mammal containing the articular disease specific fluctuation gene obtained by the manufacturing method according to claim 3, its joint, its joint

organization, or its joint.
[Claim 19] The screening approach of the articular disease accommodation medicine characterized by using the cell which constitutes the nonhuman mammal which has the capacity which produces the articular disease specific fluctuation gene product acquired by the manufacturing method according to claim 4, its joint, its joint organization, or its joint.
[Claim 20] The screening approach according to claim 18 or 19 characterized by measuring the amount of mRNA(s) corresponding to the articular disease specific fluctuation gene concerned when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint.
[Claim 21] The screening approach according to claim 18 or 19 which measures the amount of production of the articular disease specific fluctuation gene product concerned when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint.
[Claim 22] The screening approach according to claim 18 or 19 of searching the function of the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint.
[Claim 23] The kit for screening of the articular disease accommodation medicine characterized by including the cell which constitutes the nonhuman mammal containing the articular disease specific fluctuation gene obtained by the manufacturing method according to claim 3, its joint, its joint organization, or its joint.
[Claim 24] The kit for screening of the articular disease accommodation medicine characterized by including the cell which constitutes the nonhuman mammal which has the capacity which produces the joint associated-diseases gene product acquired by the manufacturing method according to claim 4, its joint, its joint organization, or its joint.
[Claim 25] Articular disease accommodation medicine obtained using an approach according to claim 18 to 22, claim 23, or the kit for screening given in 24.
[Claim 26] The remedy which comes to contain the articular disease accommodation medicine obtained using an approach according to claim 18 to 22, claim 23, or the kit for screening given in 24.
[Claim 27] The remedy according to claim 26 which is fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or prevention / therapy agent of

rheumatoid arthritis.
[Claim 28] The prevention / therapy approach of the articular disease characterized by prescribing for the patient the effective dose of the articular disease accommodation medicine obtained using an approach according to claim 18 to 22, claim 23, or the kit for screening given in 24 to mammalian.
[Claim 29] The pharmacometrics approach of the compound concerned characterized by medicating with a trial compound the cell which constitutes the nonhuman mammal obtained by the manufacturing method according to claim 1, its joint, its joint organization, or its joint.
[Claim 30] The approach according to claim 29 characterized by searching change of the cell which constitutes the nonhuman mammal when not prescribing a medicine for the patient with the case where a trial compound is prescribed for the patient, its joint, a joint organization, or a joint.
[Claim 31] The approach according to claim 29 characterized by searching the function of the cell which constitutes the nonhuman mammal when not prescribing a medicine for the patient with the case where a trial compound is prescribed for the patient, its joint, a joint organization, or a joint.
[Claim 32] The approach according to claim 29 to 31 a trial compound is a gene product.
[Claim 33] The remedy which comes to contain the compound by which drug effect was evaluated using the approach according to claim 29 to 31.
[Claim 34] The remedy according to claim 33 which is articular disease accommodation medicine.
[Claim 35] The remedy according to claim 34 which is fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or prevention / therapy agent of rheumatoid arthritis.
[Claim 36] The antibody to the gene product as which a function or drug effect was solved by the approach according to claim 8 or 29, its partial peptide, or its salt.
[Claim 37] Antisense nucleic acid to the gene as which the function was solved by the approach according to claim 8.
[Claim 38] The remedy which comes to contain an antibody according to claim 36.
[Claim 39] The remedy which comes to contain antisense nucleic acid according to claim 37.
[Claim 40] The remedy according to claim 38 or 39 which is articular disease accommodation medicine.
[Claim 41] The remedy according to claim 40 which is fracture, the

refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or prevention / therapy agent of rheumatoid arthritis.

[Claim 42] The articular disease diagnostic agent which comes to contain an antibody according to claim 36.

[Claim 43] The articular disease diagnostic agent which comes to contain antisense nucleic acid according to claim 37.

[Claim 44] The diagnostic agent according to claim 42 or 43 which is fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or a diagnostic agent of rheumatoid arthritis.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the functional analysis of a disease specific fluctuation gene. It is related with the model animal which prescribes for the patient the drug at the time of analyzing an operation in the cell which constitutes the joint of the articular disease which participates in the osteoarthritis, rheumatoid arthritis, or osteoporosis, and an articular disease specific-in more detail fluctuation gene, a joint organization, and a joint, a gene, or its gene product.
[0002]
[Description of the Prior Art] An articular disease is mainly classified into a bone disease, a chondropathy, and arthritis. There are metabolic bone diseases, such as non-metabolic bone diseases, such as fracture, bone deformation, and osteogenesis imperfecta, osteoporosis, and osteomalacia, in a bone disease. There are chronic diseases, such as osteoarthritis and rheumatoid arthritis, in a chondropathy. arthritis -- a frozen shoulder and a tendon -- there are inflammatory diseases, such as - tendon sheath and peritendinitis. If it is called an articular disease with many disease patients, the diseases (for example, rheumatoid arthritis or osteoarthritis etc.) which make denaturation of an articular cartilage the main lesion will be pointed out. For example, in the case of the chondropathy represented by the osteoarthritis with most patients, the extracellular matrix constituted by a collagen and proteoglycan is decomposed by various factors with proteoglycan and the extracellular-matrix dialytic ferment subsequently called the matrix METARO protease of collagenase-3 grade in order of a collagen. The cartilage which has covered the front face of joints, such as a knee, a jaw, an elbow, a crotch, a finger, and a jaw, by this is hardened and destroyed, and through deformation of a joint, in being critical, it results in a malfunction. It is known that the rate of the onset will increase the

osteoarthritis with aging, and the increment in the number of patients will be assumed in an aging society including the West from now on. A walk may become difficult, when the main clinical manifestation is the flexible incompetence of the knee accompanying the arthralgia, and the digestion incompetence of a jaw and symptoms develop in a knee joint or a hip joint. As a cure, in order that cartilage playback may take time amount to a cartilaginous tissue once cartilage destruction advances since the ability to regenerate is scarce, when accompanied by the intense pain, a joint total replacement arthroplasty way or an osteotomy is performed, and the method of saving a joint function is taken. The actual condition is that symptomatic therapy, such as hyaluronic acid pharmaceutical preparation and an antiinflammatory drug, is used for prevention and the therapy of the osteoarthritis from the object of pain relief, and drugs which carry out a direct action to the cell which constitutes a joint are not developed, but there is no fundamental remedy conventionally.

[0003]

[Problem(s) to be Solved by the Invention] mind [manufacture / of the model animal which prescribes the drug about remedy development, the gene, or its gene product from a viewpoint of creation of joint destructive depressant and a joint restoration remedy in this invention for the patient] -- placing -- **** -- an object [pharmacometrics / of the retrieval target / the functional analysis and pharmacometrics] -- carrying out -- an articular disease -- the manufacture approach of a model animal of prescribing a drug, a gene, or its gene product for the patient specifically and efficiently etc. is offered.

[0004]

[Means for Solving the Problem] The result of having repeated research wholeheartedly in order that this invention persons might solve the above-mentioned technical problem, The technique of cutting [technique] the ligament of the conventional knee joint and making an articular disease induce artificially (OSUTEO ground rye TISU cart REIJI) Compared with the 9th volume, 308 pages, and 2001, the direction of the technique of making an articular disease induce artificially found out that destruction of an unexpected more remarkable cartilage could be made to induce by adding the meniscectomy of a knee joint to a tibial collateral ligament, an anterior cruciate ligament, and posterior cruciate ligament cutting. this invention person came to complete this invention, as a result of repeating examination further based on these knowledge.

[0005] This invention Namely, the tibial collateral ligament of (1) nonhuman mammal (preferably Latt), an anterior cruciate ligament and a posterior cruciate ligament -- cutting -- further -- said -- the meniscus syndesmectomy model nonhuman mammal characterized by making joint

destruction induce substantially by excising the inside knee meniscus of a leg -- The meniscus syndesmectomy model nonhuman mammal containing the gene concerned characterized by medicating with a gene the nonhuman mammal obtained by the manufacturing method of the cell which constitutes the joint, its joint organization, or its joint, and the manufacturing method given in (2) above-mentioned (1), The nonhuman mammal which has the capacity which produces the gene product concerned characterized by medicating with a gene the nonhuman mammal obtained by the manufacturing method of the cell which constitutes the joint, its joint organization, or its joint, and the manufacturing method given in (3) above-mentioned (1), The manufacturing method of the cell which constitutes the joint, its joint organization, or its joint, and (4) nonhuman mammals A drug, The manufacturing method given [above-mentioned] in (1) - (3) which is the animal which can guess the drug effect or the gene function of a gene or a gene product, (5) A manufacturing method the above (2) whose gene is the ** sense DNA, ** antisense DNA, ** virus vector, or ** plasmid vector, or given in (3), (6) A manufacturing method the above (2) whose gene is an articular disease specific fluctuation gene, or given in (3), (7) How to solve the function of the gene concerned to which a function is characterized by prescribing an unknown gene for the patient, or its gene product to the nonhuman mammal obtained by the manufacturing method of the above-mentioned (1) publication, (8) The nonhuman mammal concerned when not prescribing a medicine for the patient with the case where a gene with an unknown function is prescribed for the patient, The approach of the above-mentioned (7) publication characterized by searching change of the cell which constitutes the joint, a joint organization, or a joint, (9) The nonhuman mammal concerned when not prescribing a medicine for the patient with the case where a gene with an unknown function is prescribed for the patient, The approach of the above-mentioned (7) publication characterized by searching the function of the cell which constitutes the joint, a joint organization, or a joint, (10) The nonhuman mammal obtained by the manufacturing method of the above-mentioned (1) publication, its joint, The gene characterized by including the cell which constitutes the joint organization or joint, or the kit for a functional break through of the gene product, (11) The nonhuman mammal containing the gene obtained by the manufacturing method of the above-mentioned (2) publication, The gene concerned characterized by including the cell which constitutes the joint, its joint organization, or a joint, or the kit for a functional break through of the gene product, (12) The nonhuman mammal which has the capacity which produces the gene product acquired by the manufacturing method of the above-mentioned (3) publication, The gene concerned characterized by including the cell which constitutes the joint, its joint organization, or its joint,

or the kit for a functional break through of the gene product, (13) The remedy which comes to contain the gene as which the function was solved by either an approach given in either of - (9), or above-mentioned (7) above-mentioned (10) - (12) using the kit of a publication, (14) The remedy which comes to contain the gene product of a gene with which the function was solved by either an approach given in either of - (9), or above-mentioned (7) above-mentioned (10) - (12) using the kit of a publication, (15) A remedy the above (13) which is articular disease accommodation medicine (preferably articular disease remedy), or given in (14), (16) Fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, Scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or rheumatoid arthritis (preferably) The remedy of the above-mentioned (15) publication which are prevention / therapy agents, such as the above-mentioned disease in an orthopedics field, (17) The nonhuman mammal containing the articular disease specific fluctuation gene obtained by the manufacturing method of the above-mentioned (2) publication, The screening approach of the articular disease accommodation medicine characterized by using the cell which constitutes the joint, its joint organization, or its joint, (18) The nonhuman mammal which has the capacity which produces the articular disease specific fluctuation gene product acquired by the manufacturing method of the above-mentioned (3) publication, The screening approach of the articular disease accommodation medicine characterized by using the cell which constitutes the joint, its joint organization, or its joint, (19) It can set, when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint. The above (17) characterized by measuring the amount of mRNA(s) corresponding to the articular disease specific fluctuation gene concerned, or the screening approach given in (18), (20) It can set, when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint. The above (17) which measures the amount of production of the articular disease specific fluctuation gene product concerned, or the screening approach given in (18), (21) [when not adding with the case where a trial compound is added to the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint] The above (17) which searches the function of the cell which constitutes the nonhuman mammal concerned, its joint, its joint organization, or its joint, or the screening approach given in (18), (22) The nonhuman mammal containing the articular disease specific fluctuation gene obtained by the manufacturing method of the above-mentioned (2)

publication, The kit for screening of the articular disease accommodation medicine characterized by including the cell which constitutes the joint, its joint organization, or its joint, (23) The nonhuman mammal which has the capacity which produces the joint associated-diseases gene product acquired by the manufacturing method of the above-mentioned (3) publication, its joint, its joint organization, or its joint The kit for screening of the articular disease accommodation medicine characterized by including the cell to constitute, (24) Articular disease accommodation medicine obtained using the kit for screening of an approach given in either of - (21), the above-mentioned above (22), or above-mentioned (17) (23) publication, (25) The remedy which comes to contain the articular disease accommodation medicine obtained using the kit for screening of an approach given in either of - (21), the above-mentioned above (22), or above-mentioned (17) (23) publication, (26) Fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, Scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTÓ disease, a rigidity myelitis, hypertrophic arthritis, or rheumatoid arthritis (preferably) The remedy of the above-mentioned (25) publication which are prevention / therapy agents, such as the above-mentioned disease in an orthopedics field, (27) The prevention / therapy approach of the articular disease characterized by prescribing for the patient the effective dose of the articular disease accommodation medicine obtained using the kit for screening of an approach given in either of - (21), the above-mentioned above (22), or above-mentioned (17) (23) publication to mammalian, (28) The nonhuman mammal obtained by the manufacturing method of the above-mentioned (1) publication, its joint, The pharmacometrics approach of the compound concerned characterized by medicating with a trial compound the cell which constitutes the joint organization or its joint, (29) The nonhuman mammal when not prescribing a medicine for the patient with the case where a trial compound is prescribed for the patient, The approach of the above-mentioned (28) publication characterized by searching change of the cell which constitutes the joint, a joint organization, or a joint, (30) The nonhuman mammal when not prescribing a medicine for the patient with the case where a trial compound is prescribed for the patient, The approach of the above-mentioned (28) publication characterized by searching the function of the cell which constitutes the joint, a joint organization, or a joint, (31) The approach given [above-mentioned] in (28) - (30) a trial compound is a gene product, (32) The remedy which comes to contain the compound by which drug effect was evaluated by either of above-mentioned (28) - (31) using the approach of a publication, (33) The remedy of the above-mentioned (32) publication which is articular disease accommodation medicine (preferably articular disease

remedy), (34) The fracture in an orthopedics field, refracture, bone deformation / deformation spondylosis, An osteosarcoma, myeloma, the osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, Rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or rheumatoid arthritis (preferably) The remedy of the above-mentioned (33) publication which are prevention / therapy agents, such as the above-mentioned disease in an orthopedics field, (35) The gene product as which a function or drug effect was solved by the approach the above (7) or given in (28), The antibody to the partial peptide or its salt, the antisense nucleic acid to the gene as which the function was solved by the approach given in (36) above-mentioned (7), (37) The remedy which comes to contain the antibody of the above-mentioned (35) publication, the remedy which comes to contain antisense nucleic acid given in (38) above-mentioned (36), (39) A remedy the above (37) which is articular disease accommodation medicine (preferably articular disease remedy), or given in (38), (40) Fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, Scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or rheumatoid arthritis (preferably) The remedy of the above-mentioned (39) publication which are prevention / therapy agents, such as the above-mentioned disease in an orthopedics field, (41) The articular disease diagnostic agent which comes to contain the antibody of the above-mentioned (35) publication, the articular disease diagnostic agent which comes to contain antisense nucleic acid given in (42) above-mentioned (36), And (43) fracture, the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, The osteogenesis imperfecta, scoliosis, a bone deficit, osteoporosis, osteomalacia, rickets, fibrous ostitis, A diagnostic agent the above (41) which is diagnostic agents, such as renal rickets, a ****-CHIETTO disease, a rigidity myelitis, hypertrophic arthritis, or rheumatoid arthritis (the above-mentioned disease [in / preferably / an orthopedics field]), or given in (42) etc. is offered.

[0006]

[Embodiment of the Invention] [Manufacturing method of a meniscus syndesmectomy model nonhuman mammal] The manufacturing method of the meniscus syndesmectomy model nonhuman mammal (it is hereafter written as a model animal) of this invention is substantially characterized by making an articular disease induce artificially and making destruction of a remarkable cartilage induce by this by adding an inside meniscectomy to cutting of three ligaments of the tibial collateral ligament of the knee joint of a nonhuman mammal, an anterior cruciate ligament, and a posterior cruciate ligament. the model animal obtained by this manufacturing method -- an object [

pharmacometrics / of a retrieval target / the functional analysis and pharmacometrics] -- carrying out -- an articular disease -- it becomes the object which prescribes a drug, a gene, or its gene product for the patient specifically and efficiently. As a nonhuman mammal, for example, a guinea pig, Latt, a mouse, a rabbit, Buta, a sheep, a cow, an ape, etc. are mentioned, especially, a mite is desirable, rodents, such as Latt and a mouse, are especially desirable, and especially Latt is suitable. opening of the knee joint is carried out to the meniscectomy of a knee joint, and it is with it about a part of cartilaginous meniscus which intervenes between the bones which constitute the upper and lower sides of the cavum articulare -- it is -- it points out cutting all off. Thereby, contact of the bones which the movability of a joint is spoiled and constitute the upper and lower sides takes place, and destruction of the cartilage which exists in epiphysis takes place. a meniscectomy -- the very thing -- it can carry out using the approach according to a well-known approach (toxicology cull PASOROJI, the 27th volume, 134 pages, 1999), for example, the manufacture approach of an arthritis model animal, or it. As matter used as the object for administration, a drug, a gene, gene products (an example, protein, peptide, etc.), etc. are used for a meniscus syndesmectomy model animal. It will not be limited especially if it is the matter which has a therapy and a preventive effect to various diseases, such as not only an articular disease but inflammation, as a drug. Specifically, the drug by which adoption is carried out to the Japanese pharmacopoeia is used. Furthermore, as a drug, a trial compound with an unknown pharmacological action, a drug with the unknown second remedy application, etc. can also be used. As a trial compound, living body origin nonpeptidic compounds (sugar, lipid, etc.), a synthetic compound (a peptide is included), a microorganism culture, a cell extract, a vegetable extract, an animal tissue extract, etc. may be used, and these compounds may be new molecular entities and may be well-known compounds, for example. As a gene, you may be any of a gene with an unknown function, and the gene as which the function is solved, and may be any of genomic DNA and cDNA. Moreover, genes may be any of Sense DNA and an antisense DNA. Moreover, although this DNA can also be independently prescribed for the patient, it is the form of liposome or can be used, being able to insert in suitable vectors [, such as a virus vector; plasmid vector,], such as a retrovirus vector, an adenovirus vector, and an adenovirus-associated virus vector. Furthermore, these genes may be gene fragments which may carry out the code of the protein or the peptide of an overall length, and carry out the code of some of protein or peptides. As a gene product, you may be any of protein and a peptide. Moreover, both a gene product with an unknown function and the gene product with which the function is solved can be used.

[0007] Although especially the sequence of the technique is not limited, it

cuts, cutting of the tibial collateral ligament for incision of the skin and cavum-articulare exposure, cutting of an anterior cruciate ligament, and a posterior cruciate ligament rank second, and, as for the manufacturing method of the model animal of this invention, the approach of the suture for closeout of an inside meniscectomy and the cavum articulare is usually specifically used. As long as the same approach is substantially used for the manufacturing method of this invention with this concrete approach, the approach approach etc. can be changed suitably. That is, about 1-4 operations of a nonhuman mammal usually consist of each about 15-30 technique preferably, and if these technique has the same bases, it can be transposed to the technique which each experimenter changed and was acquired. These technique is acquirable from well-known books or well-known reference etc. Therefore, the model animal manufacture approach of this invention is changeable suitably, if three desmotomy shown in the point of an object nonhuman mammal and an inside meniscectomy are performed using the same approach as substantially as the above-mentioned concrete approach. As extent of an alteration, it is the range which has about 95% or more of identity most preferably about 90% or more 80% or more of good better **** the above-mentioned creation approach and about 70% or more, for example. The case where it has about 95% or more of identity most preferably is [80% or more of good better ****] more preferably desirable about 70% or more about 90% or more as a whole including the process which excises an inside meniscus where three ligaments of the knee joint of a nonhuman mammal are cut especially. using the manufacturing method of such this invention -- a joint -- a joint animal used in disease modeling can be manufactured specifically and efficiently. Usually, even if it deals with attaching a blemish to an articular cartilage etc., it does not become the symptoms of the osteoarthritis (OA), and a mite (especially Latt) cures immediately in many cases. However, according to the manufacturing method of this invention, even if it uses mites, such as Latt, OA model animal is efficiently producible. Moreover, since a mite can be used, there is an advantage that the amount of the compound with which per weight is medicated, or a gene can be saved. From the model animal produced by the manufacturing method of this invention, the cell which constitutes a joint, a joint organization, or a joint can be extracted in a stock-in-trade. As a cell which constitutes a joint, osteocyte, osteoblast, an osteoclast, chondrocyte, a joint synovial cell, fibroblast, etc. are mentioned.

[0008] [Manufacturing method of the model animal containing a gene] The manufacturing method of the model animal containing the gene of this invention should just make the gene described above to the model animal of above-mentioned this invention contain by a virus vector etc. By using this manufacturing method, the model animal which has the capacity which

produces the model animal containing the gene concerned or the gene product concerned can be manufactured. Moreover, the cell which constitutes the cell which constitutes the joint, joint organization, or joint containing the gene concerned from these model animals or the joint which has the capacity which produces the gene product concerned, a joint organization, or a joint can be extracted in a stock-in-trade.

[Manufacturing method of the cell which constitutes the joint containing a gene] The manufacturing method of the cell which constitutes the joint containing the aforementioned gene is characterized by excising an inside meniscus substantially, where three ligaments of a tibial collateral ligament, an anterior cruciate ligament, and a posterior cruciate ligament are cut in the knee joint of a nonhuman mammal. Concrete actuation should just make the gene described above to the model animal of above-mentioned this invention contain by a virus vector etc. By using this manufacturing method, the cell which constitutes the joint containing the gene concerned, or the cell which constitutes the joint which has the capacity which produces the gene product concerned can be manufactured. The approach of isolating the cell which constitutes the joint concerned from a joint is well-known, for example, OSUTEO ground rye TISU, in itself. The approach according to the approach or it which is indicated by cull tee REJI (the 9th volume, 73 - 84 pages, 2001) is used.

[0009] [Approach of solving the function of a gene with an unknown function] The functional break-through approach of the gene of this invention solves the function of the gene concerned by medicating the model animal of this invention with a gene with an unknown function. You may be any of genomic DNA and cDNA as the function described above as an unknown gene. Moreover, the gene concerned may be a gene fragment which may carry out the code of the protein or the peptide of an overall length, and carries out the code of some of protein or peptides. As a function, the function about the movability of a joint is mentioned and, more specifically, joint destructive depressant action, a joint restoration operation, etc. are mentioned, for example. A break through of a function For example, the model animal when not prescribing a medicine for the patient with the case where a gene with unknown (1) function is prescribed for the patient, Change of the function of the cell which constitutes the joint, a joint organization, or a joint is searched (although any of assay, detection, or measurement are sufficient, it measures preferably), (2) It is carried out by searching the function of the cell which constitutes the model animal when not prescribing a medicine for the patient with the case where a gene with an unknown function is prescribed for the patient, its joint, a joint organization, or a joint (it measuring preferably, although any of assay, detection, or measurement are sufficient) etc. Setting to the approach of (1), retrieval (although any of assay, detection, or

measurement are sufficient, it measures preferably) of the function of a joint is for example, ground rye TISU. It can carry out to RYUMATIZUMU (Arthritis Rheum, the 44th volume, 1071 - 1081 pages, 2001) using the approach of a publication. Retrieval (although any of assay, detection, or measurement are sufficient, it measures preferably) of the function of the cell which constitutes a joint in the approach of (2) is for example, ground rye TISU. It can carry out to RYUMATIZUMU (Arthritis Rheum, the 44th volume, 1071 - 1081 pages, 2001) using the approach of a publication. culture of the cell which constitutes a joint -- the very thing -- it can carry out using a well-known approach, for example, an approach given in ground litchi SURYUMATIZUMU (Arthritis Rheum, the 44th volume, 1071 - 1081 pages, 2001). Furthermore, the function of the cell which constitutes a joint can be more efficiently solved by cultivating the cell which constitutes a joint under application-of-pressure conditions, or cultivating it under fatal conditions. The bottom of an application-of-pressure condition points out conditions as if the bone lapsed into the application-of-pressure condition by adding centrifugal actuation etc. in the process in which the cell which constitutes a joint, for example, osteoblast, is cultivated. Under application-of-pressure conditions, osteoblast will receive application-of-pressure stress, a cell will arrange and transmit a signal, and the means against stress will be prepared. Prescribing a toxic high anticancer agent (for example, adriamycin) for the patient as fatal conditions to the cell which constitutes clearance of a blood serum and a joint etc. is mentioned.

[0010] The kit for a functional break through of this invention contains the cell which constitutes the cell which constitutes the model animal containing the gene concerned, its joint, its joint organization, or its joint or the model animal which has the capacity which produces the gene product concerned, its joint, its joint organization, or a joint. The following are mentioned as an example of the kit for a functional break through of this invention.

1. What added 0.05% of bovine serum albumin (sigma company make) to the buffer solution for reagent ** measurement, and buffer-solution Hanks' Balanced Salt Solution for washing (Gibco make). or it carries out filtration sterilization with the filter of 0.45 micrometers of apertures and saves at 4 degrees C -- or business -- the time -- you may prepare .

** the cell which constitutes the joint which has the capacity which produces the cell which constitutes the joint containing the gene concerned, or the gene product concerned -- the cell which constitutes the joint of these -- 12 hole plate -- 5x105 pieces / hole -- a passage -- carrying out -- 37 degrees C, 5%CO2, and the thing cultivated for two days by air 95%. By using the above-mentioned functional break-through approach or the kit for a functional break through, the function of a joint when the function contains compared with the joint which does not contain the unknown gene, and the

function of the cell which constitutes a joint can judge preferably that the gene concerned has a joint function acceleration (or improvement or sthenia) operation about 30% or more about 20% or more, when it goes up about 50% or more more preferably. Preferably, about 30% or more, the function of a joint when the function contains on the other hand compared with the joint which does not contain the unknown gene, and the function of the cell which constitutes a joint can judge that the gene concerned has a joint depression operation about 20% or more, when it falls about 50% or more more preferably. As for the solved gene, it is useful respectively as a joint function regulatory gene that having a joint function acceleration operation has the solved gene or joint depression operation as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy). As for the solved gene, it is useful as a bone or a prevention / therapy agent of an articular disease to have a joint function acceleration operation especially. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, having a joint function acceleration operation can use the solved gene for the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer.

[0011] When using the gene as which the function was solved as the above-mentioned remedy constituent, after inserting the gene concerned in suitable independent or vectors, such as a retrovirus vector, an adenovirus vector, and an adenovirus-associated virus vector, it can carry out according to a stock-in-trade. The gene concerned remains as it is, or can be prescribed for the patient with a catheter like a gene gun or a hydro gel catheter with the adjuvant for acceleration of intake. For example, the gene concerned can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with the gene concerned with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be

accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. A dosage with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained. As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate 80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing agent, for example. Moreover, the above-mentioned remedy constituent may be blended with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution. Thus, the remedy constituent obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to mammalians (for example, Homo sapiens, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example. Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in an osteoarthritis patient, about 0.1mg - 100mg per day of about 1.0-50mg of doses of the gene concerned is about 1.0-20mg more preferably (as 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / an osteoarthritis patient (as 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which

converted into per 60kg also in other animals can be prescribed for the patient.

[0012] The [screening approach of a remedy candidate compound] When the function of the gene with which the model animal of this invention is medicated is solved, a remedy candidate compound can be screened using the following approaches.

[The screening approach of the remedy candidate compound using the cell which constitutes a joint] This invention offers the screening approach of the joint function accommodation medicine characterized by to use the cell which constitutes the joint of the model animal of this invention which has the capacity which produces for example, the screening approach of the joint function accommodation medicine characterized by to use the cell which constitutes the joint of the model animal of this invention containing (1) gene and (2) gene products. The above-mentioned thing and the same thing are used as a cell which constitutes the joint concerned. Moreover, culture of the cell which constitutes a joint as well as the above can be performed. As a gene, articular disease specific fluctuation genes which participate in a joint function, such as a gene and a joint function regulatory gene, are used. More specifically, it is KONEKUTIBU. Tissue A research (Connect Tissue Res 41 volume, 175 - 184 pages, 2000) etc. is used. this screening approach -- for example, the above -- the same -- ** -- giving a stimulus to the cell which constitutes the joint concerned under application-of-pressure conditions, and ** -- it can carry out by cultivating the cell which constitutes the joint concerned under fatal conditions etc. Prescribing a toxic high anticancer agent (an example, adriamycin) for the patient as the bottom of a fatal condition to the cell which constitutes clearance of a blood serum and a joint etc. is mentioned.

[0013] more -- concrete -- this screening approach -- (1) -- measuring the amount of mRNA(s) corresponding to the gene concerned when not adding with the case where a trial compound is added to the cell which constitutes the joint concerned, and (2) -- it can carry out by measuring the amount of production of the gene product concerned when not adding with the case where a trial compound is added to the cell which constitutes the joint concerned etc. [for example,] As a trial compound, living body origin nonpeptidic compounds (sugar, lipid, etc.), a synthetic compound (a peptide is included), a microorganism culture, a cell extract, a vegetable extract, an animal tissue extract, etc. may be used, and these compounds may be new molecular entities and may be well-known compounds, for example. the amount of manifestations of mRNA -- the very thing -- it can measure according to the approach according to a well-known approach, for example, approaches, such as Northern blotting, Reverse transcription-polymerase chain reaction (RT-PCR), and TaqMan polymerasechain reaction, or it. the

amount of production of a gene product -- the very thing -- it can measure by the well-known approach, for example, the approach using an antibody, the approach using a chromatography, etc. The thing as the kit for a functional break through of the gene described above including the cell which constitutes the joint concerned with this same kit for screening is used. By using the above-mentioned screening approach or the kit for screening, the amount of mRNA(s) at the time of prescribing a medicine for the patient and the amount of gene products can judge preferably that, as for the trial compound concerned, it has a joint function acceleration operation when it goes up about 50% or more more preferably about 30% or more about 20% or more compared with the case where a trial compound is not prescribed for the patient. On the other hand, compared with the case where a trial compound is not prescribed for the patient, preferably, the amount of mRNA(s) at the time of prescribing a medicine for the patient and the amount of gene products can judge that the trial compound concerned has a joint depression operation about 30% or more about 20% or more, when it falls about 50% or more more preferably. As for a trial compound, it is useful respectively as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy), to have a joint function acceleration operation or a joint depression operation. Especially the trial compound that has a joint function acceleration operation is useful as a bone or a prevention / therapy agent of an articular disease. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, the trial compound which has a joint function acceleration operation is applicable to the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer.

[0014] Thus, when using the compound obtained using the above-mentioned screening approach or the kit for screening as the above-mentioned remedy constituent, it can pharmaceutical-preparation-ize using a stock-in-trade. For example, the compound concerned can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as

the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with the compound concerned with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. A dosage with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained. As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate 80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing agent, for example. Moreover, the above-mentioned remedy constituent may be blended with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution. Thus, the remedy constituent obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to mammalians (for example, Homo sapiens, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example. Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in an osteoarthritis patient, about 0.1mg - 100mg per day of about 1.0-50mg of doses of the compound concerned is about 1.0-20mg more preferably (as 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / an

osteoarthritis patient (as 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per 60kg also in other animals can be prescribed for the patient.

[0015] [The screening approach of a model animal or the remedy candidate compound using the joint] This invention offers the screening approach of the joint function accommodation medicine characterized by using the model animal of this invention which has the capacity which produces for example, the screening approach of the joint function accommodation medicine characterized by using the model animal of this invention containing (1) gene, or its joint and (2) gene products, or its joint. The same thing as the above is used as the model concerned or its joint. As a trial compound, living body origin nonpeptidic compounds (sugar, lipid, etc.), a synthetic compound (a peptide is included), a microorganism culture, a cell extract, a vegetable extract, an animal tissue extract, etc. may be used, and these compounds may be new molecular entities and may be well-known compounds, for example. As a gene, articular disease specific fluctuation genes which participate in a joint function, such as a gene and a joint function regulatory gene, are used. More specifically, it is KONEKUTIBU. Tissue A research (Connect Tissue Res 41 volume, 175 - 184 pages, 2000) etc. is used. This screening approach can be enforced by searching the joint function of the model animal concerned or its joint (it measuring preferably, although any of assay, detection, or measurement are sufficient), when not adding with the case where a trial compound is added to the model animal concerned. Measurement of a joint function can be carried out like the above. By using this screening approach, the joint function at the time of prescribing a medicine for the patient can judge preferably that, as for the trial compound concerned, it has a joint function acceleration operation when it goes up about 50% or more more preferably about 30% or more about 20% or more compared with the case where a trial compound is not prescribed for the patient. Preferably, about 30% or more, the joint function at the time of on the other hand prescribing a medicine for the patient compared with the case where a trial compound is not prescribed for the patient, and the function of the cell which constitutes a joint can judge that the trial compound concerned has a joint depression operation about 20% or more, when it falls about 50% or more more preferably. The trial compound which has a joint function acceleration operation or a joint depression operation is useful respectively as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy). Especially the

trial compound that has a joint function acceleration operation is useful as a bone or a prevention / therapy agent of an articular disease. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, the trial compound which has a joint function acceleration operation is applicable to the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer.

[0016] Thus, when using the compound obtained using the above-mentioned screening approach or the kit for screening as the above-mentioned remedy constituent, it can pharmaceutical-preparation-ize using a stock-in-trade. For example, the compound concerned can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with the compound concerned with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. A dosage with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained. As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example,

D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate 80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing agent, for example. Moreover, the remedy constituent of ****** may be blended with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution. Thus, the remedy constituent obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to mammalians (for example, Homo sapiens, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example. Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in an osteoarthritis patient, about 0.1mg - 100mg per day of about 1.0-50mg of doses of the compound concerned is about 1.0-20mg more preferably (as 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / an osteoarthritis patient (as 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per 60kg also in other animals can be prescribed for the patient.

[0017] [Gene therapy method] The joint function of mammalian can be adjusted by medicating mammalian with the effective dose of the joint function regulatory gene as which the function was solved using the functional break-through approach of the gene of this invention. In an osteoarthritis patient, it is usually preferably convenient [the dose of the gene concerned to mammalian], although it is different with the symptom for administration etc. to medicate the direct cavum articulare with about about 0.1-20mg about about 0.1-10mg more preferably about about 0.01-30mg, for example (as 60kg). The amount which converted into per 60kg also in other animals can be prescribed for the patient.

[0018] The [assessment approach of a compound] This invention offers the pharmacometrics approach of the compound concerned characterized by medicating with a trial compound the cell which constitutes the model animal

of (1) this invention, its joint, its joint organization, or its joint. As a trial compound, things other than a gene, for example, a gene product, living body origin nonpeptidic compounds (sugar, lipid, etc.), a synthetic compound (a peptide is included), a microorganism culture, a cell extract, a vegetable extract, an animal tissue extract, etc. may be used, and these compounds may be new molecular entities and may be well-known compounds. When using a gene, it can carry out like the functional break-through approach of the above mentioned gene. The medication method of a trial compound is the same as the medication method of above mentioned this invention. The model animal when not prescribing a medicine for the patient with the case where (1) trial compound is prescribed for the patient, by this pharmacometrics approach, for example, Change of the function of the cell which constitutes the joint, its joint organization, or its joint is searched (or assay, detection, or measurement), (2) The drug effect of a trial compound is evaluated by searching the function of the cell which constitutes the model animal when not prescribing a medicine for the patient with the case where a trial compound is prescribed for the patient, its joint, its joint organization, or its joint (or assay, detection, or measurement) etc. By the approach of the above (2), pharmacometrics can be more effectively performed giving a stimulus and, cultivating the cell which constitutes ** joint under application-of-pressure conditions, for example, by cultivating the cell which constitutes ** joint under fatal conditions, etc. Prescribing a toxic high anticancer agent (an example, adriamycin) for the patient as fatal conditions to the cell which constitutes clearance of a blood serum and a joint etc. is mentioned. This pharmacometrics approach can be enforced like the functional break-through approach of the gene of above mentioned this invention, and the screening approach of a remedy candidate compound.

[0019] By using the above-mentioned pharmacometrics approach, the function of the cell which constitutes the joint function or joint at the time of prescribing a medicine for the patient etc. can judge preferably that, as for the trial compound concerned, it has a joint function acceleration operation when it goes up about 50% or more more preferably about 30% or more about 20% or more compared with the case where a trial compound is not prescribed for the patient. Preferably, about 30% or more, the function of the cell which constitutes the joint function or joint at the time of on the other hand prescribing a medicine for the patient compared with the case where a trial compound is not prescribed for the patient can judge that the trial compound concerned has a joint depression operation about 20% or more, when it falls about 50% or more more preferably. The trial compound which has a joint function acceleration operation or a joint depression operation is useful respectively as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy). Especially the

trial compound that has a joint function acceleration operation is useful as a bone or a prevention / therapy agent of an articular disease. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, the trial compound which has a joint function acceleration operation is applicable to the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer. Thus, when using the compound obtained using the above-mentioned screening approach or the kit for screening as the above-mentioned remedy constituent, it can pharmaceutical-preparation-ize using a stock-in-trade. For example, the compound concerned can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with the compound concerned with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. A dosage with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained. As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the

adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate 80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing agent, for example. Moreover, the above-mentioned remedy constituent may be blended with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution. Thus, the remedy constituent obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to mammalians (for example, Homo sapiens, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example. Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in an osteoarthritis patient, about 0.1mg - 100mg per day of about 1.0-50mg of doses of the compound concerned is about 1.0-20mg more preferably (as 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / an osteoarthritis patient (as 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per 60kg also in other animals can be prescribed for the patient.

[0020] [Antibody] This invention offers the antibody to the gene product with which a function or drug effect became clear, its partial peptide, or its salt by using the above-mentioned functional break-through approach or the above-mentioned pharmacometrics approach of this invention. As long as the antibody of this invention is an antibody which can recognize the gene product concerned, its partial peptide, or its salt, it may be any of a polyclonal antibody and a monoclonal antibody. the antibody to the gene product concerned, its partial peptide, or its salt (it is hereafter written as the gene product concerned) -- the gene product concerned -- as an antigen -- using -- the very thing -- it can manufacture according to the manufacturing method of a well-known antibody or antiserum.

[0021] [Production of a monoclonal antibody]

(a) The part in which an antibody production is possible is medicated with this production this gene product of a monoclonal antibody production cell

with itself or support, and a diluent by administration to mammalian. In order to raise antibody production ability on the occasion of administration, a complete Freund's adjuvant and an incomplete Freund's adjuvant may be prescribed for the patient. Administration is usually performed about a total of 2 to 10 times by a unit of 1 time every 2-6 weeks. As mammalian used, although an ape, a rabbit, a dog, a guinea pig, a mouse, Latt, a sheep, and a goat are mentioned, a mouse and Latt are used preferably, for example. A monoclonal antibody production hybridoma can be prepared by choosing the individual in which antibody titer was accepted from the homeotherm by which immunity was carried out in the antigen, for example, a mouse, on the occasion of production of a monoclonal antibody production cell, extracting a spleen or lymph gland two - five days after the last immunity, and uniting with a myeloma cell the antibody forming cell contained in them. Measurement of the antibody titer in antiserum can be performed by measuring the activity of the indicator agent combined with the antibody, after making an after-mentioned labeling gene product and antiserum react. Fusion actuation can be carried out according to a known approach [Nature (Nature), 256 volumes, and 495 pages (1975)], for example, the approach of Kohler and Milstein. As a fusion accelerator, although a polyethylene glycol (PEG), a Sendai virus, etc. are mentioned, PEG is used preferably, for example. As a myeloma cell, although NS-1, P3U1, SP2/0, etc. are mentioned, P3U1 is used preferably, for example. The desirable ratio of the number of antibody forming cells (spleen cell) and the number of myeloma cells which are used is 1:1 to about 20:1, and it is added by the concentration whose PEG (preferably PEG1000-PEG6000) is about 10 - 80%, and it can carry out efficiently about 20-40 degrees C of cell fusion by incubating for about 1 - 10 minutes at about 30-37 degrees C preferably. Although various approaches can be used for screening of a monoclonal antibody production hybridoma for example, the solid phase (an example --) to which the antigen of the gene product concerned was made to stick with direct or support The anti-immunoglobulin antibody which added the hybridoma culture supernatant to the microplate and then carried out the indicator with the radioactive substance, the enzyme, etc. (when the cell used for cell fusion is a mouse) Protein A is added or an anti-mouse immunoglobulin antibody is used. A hybridoma culture supernatant is added to the solid phase to which the approach, the anti-immunoglobulin antibody, or protein A which detects the monoclonal antibody combined with solid phase was made to stick. The gene product concerned which carried out the indicator with the radioactive substance, an enzyme, etc. is added, and the method of detecting the monoclonal antibody combined with solid phase etc. is mentioned. sorting of a monoclonal antibody -- the very thing -- it can carry out by the culture medium for well-known or the animal cells which

usually added HAT (hypoxanthine, aminopterin, thymidine) although it could carry out according to the approach according to it etc. As sorting and a culture medium for breedings, as long as it can grow a hybridoma, what kind of culture medium may be used. For example, RPMI1640 culture medium which contains 10 - 20% of fetal calf serum preferably, the GIT culture medium (Wako Pure Chem Industry) containing 1 - 10% of fetal calf serum, or the serum free medium for hybridoma culture (SFM-101 and NISSUI PHARMACEUTICAL CO., LTD.) can be used 1 to 20%. 20-40 degrees C of culture temperature are usually about 37 degrees C preferably. Culture time amount is usually one week - two weeks preferably for five days to three weeks. Culture can usually be performed under 5% carbon dioxide gas. The antibody titer of a hybridoma culture supernatant can be measured like measurement of the antibody titer in the above-mentioned antiserum.
(b) Separation purification of the purification monoclonal antibody of a monoclonal antibody can be performed according to the separation purification method [the specific purification method which extracts only an antibody with activity adsorbents, such as an example, a salting-out method, a alcohol precipitation method, isoelectric point settling, an electrophoresis method, the adsorption-and-desorption method by the ion exchanger (an example, DEAE), an ultracentrifugal method, gel filtration, antigen joint solid phase, protein A, or Protein G, is made to dissociate association, and obtains an antibody] of an immunoglobulin like separation purification of the usual polyclonal antibody.
[0022] [Production of a polyclonal antibody] The polyclonal antibody of this invention can be manufactured according to well-known in itself or the approach according to it. For example, the complex of the immunogen (the gene product concerned) and carrier protein is built, immunity is performed to mammalian like the manufacturing method of the above-mentioned monoclonal antibody, the antibody inclusion to the gene product concerned is extracted from this immune animal, and it can manufacture by performing separation purification of an antibody. It is related with the complex of the immunogen and carrier protein which are used in order to carry out immunity of the mammalian. The class of carrier protein, and the mixing ratio of a carrier and hapten If an antibody is efficiently made to the hapten which the carrier was made to construct a bridge and carried out immunity Although what kind of thing may be made to construct a bridge by what kind of ratio, about 0.1-20 and the method of making it KAPURU [about one to 5 rate] preferably are used, for example to hapten 1 by the weight ratio in bovine serum albumin, the cow thyroglobulin, keyhole limpet hemocyanin, etc. Moreover, although various condensing agents can be used for coupling of hapten and a carrier, the activity ester reagent containing glutaraldehyde, a carbodiimide, maleimide activity ester, a thiol group, and a JICHIOBIRIJIRU

radical etc. is used. The part in which an antibody production is possible is medicated with a condensation product with itself or support, and a diluent to a homeotherm. In order to raise antibody production ability on the occasion of administration, a complete Freund's adjuvant and an incomplete Freund's adjuvant may be prescribed for the patient. administration -- usually -- every 1 time per about 2-6 weeks, and a total -- it can carry out about about 3 to 10 times. The blood of the mammalian by which immunity was carried out by the above-mentioned approach, ascites, etc. can extract a polyclonal antibody from blood preferably. Measurement of the polyclonal antibody titer in antiserum can be measured like measurement of the antibody titer in the above-mentioned blood serum. Separation purification of a polyclonal antibody can be performed according to the separation purification method of the same immunoglobulin as separation purification of the above-mentioned monoclonal antibody.

[0023] Since the antibody of this invention can recognize the gene product concerned specifically, it can be used for the quantum of the gene product concerned in sample liquid, especially the quantum by sandwiches immunoassay, etc. Namely, this invention makes an antibody, and the sample liquid and the labeling gene product of for example, (i) this invention react competitively. The assay of the gene product concerned in the sample liquid characterized by measuring the rate of the labeling gene product combined with this antibody, (ii) After making the antibody of this invention which insolubilized on sample liquid and support, and the labeled antibody of this invention react simultaneous or continuously, the assay of the gene product concerned in the sample liquid characterized by measuring the activity of the indicator agent on insolubilization support is offered. In the above (ii), one antibody is an antibody which recognizes N edge of the gene product concerned, and it is desirable that it is the antibody to which the antibody of another side reacts to C edge of the gene product concerned. The gene product concerned can be measured using the monoclonal antibody (the monoclonal antibody of this invention may be called hereafter) to the gene product concerned, and also detection by organization dyeing etc. can also be performed. The antibody molecule itself may be used for these objects, and F(ab') 2, Fab', or the Fab fraction of an antibody molecule may be used for them. Especially the measuring method using the antibody to the gene product concerned should not be restricted, and as long as it is chemical or a measuring method computed from the standard curve which detected by the physical means and produced this using the standard solution containing the antigen of a known amount about the amount of the antibody corresponding to the amount of antigens in measured liquid (for example, the amount of gene products concerned), an antigen, or the antibody-antigenic complex, which measuring method may be used for it. For example, although

a nephrometry, the competing method, an immunometric method, and a sandwich technique are used suitably, it is desirable especially to use the sandwich technique indicated later in respect of sensibility and singularity. As an indicator agent used for the measuring method using a marker, radioisotope, an enzyme, a fluorescent material, photogene, etc. are used, for example. As radioisotope, [125I], [131I], [3H], [14C], etc. are used, for example. As the above-mentioned enzyme, it is stable, and the big thing of specific activity is desirable, for example, the beta-galactosidase, the beta-glucosidase, alkaline phosphatase, a par oxidase, a malate dehydrogenase, etc. are used. As a fluorescent material, fluorescamine, full ORESSEN isothiocyanate, etc. are used, for example. As photogene, luminol, a luminol derivative, luciferin, lucigenin, etc. are used, for example. Furthermore, a biotin-avidin system can also be used for association with an antibody or an antigen, and an indicator agent.

[0024] The approach using the chemical bond used for using physical adsorption, and usually insolubilizing and fixing protein or an enzyme in insolubilization of an antigen or an antibody may be used. As support, synthetic resin, such as insoluble polysaccharide, such as agarose, a dextran, and a cellulose, polystyrene, polyacrylamide, and silicon, or glass is used, for example. After making sample liquid react to the monoclonal antibody of this invention which insolubilized in the sandwich technique (primary response) and making the monoclonal antibody of this invention which labeled further react (secondary response), the quantum of the amount of receptor protein of this invention in sample liquid can be carried out by measuring the activity of the indicator agent on insolubilization support. A primary response and a secondary response may be performed in order of reverse, or may be performed simultaneously, may shift time amount and may perform it. A labeling agent and the approach of insolubilization can apply to above them correspondingly. Moreover, in the immunoassay by the sandwich technique, the number of the antibodies used for the antibody for solid phase or the antibody for indicators does not necessarily need to be one, and they may use the mixture of two or more kinds of antibodies for the object of raising sensitometry. In the measuring method of the gene product concerned by the sandwich technique of this invention, the antibody in which the part where the gene product concerned combines the monoclonal antibody of this invention used for a primary response and a secondary response is different from each other is used preferably. That is, when, as for the antibody used for a primary response and a secondary response, the antibody used by the secondary response recognizes C edge of receptor protein, the antibody which the antibody used by the primary response is desirable, and recognizes N edge except C edge is used. The monoclonal antibody of this invention can be used for gaging systems, for example, the competing method,

immunometric methods, or nephrometries other than a sandwich technique etc. By the competing method, after making the antigen and labelled antigen in sample liquid react competitively to an antibody, the labelled antigen (B) combined with the labelled antigen, and (unreacted F) and an unreacted antibody is separated (B/F separation), either amount of indicators of B and F is measured, and the quantum of the amount of antigens in sample liquid is carried out. The solid phase-ized method using [the 1st antibody] a solid phase-ized antibody as the 2nd antibody using the thing of fusibility is used for this reacting method in B/F separation, using a solid phase-ized antibody as the liquid phase process using the 2nd antibody to a polyethylene glycol and the above-mentioned antibody etc., and the 1st antibody, using a fusibility antibody as an antibody.

[0025] In an immunometric method, after carrying out the competitive reaction of the antigen and solid phase-ized antigen in sample liquid to the labeling antibody of a constant rate, separating solid phase and the liquid phase, or making the antigen in sample liquid, and the labeling antibody of an excessive amount react, then adding a solid phase-ized antigen and combining an unreacted labeling antibody with solid phase, solid phase and the liquid phase are separated. Next, the amount of indicators of one of phases is measured, and the quantum of the amount of antigens in sample liquid is carried out. Moreover, in a nephrometry, the amount of the produced insoluble sediment is measured within gel and in a solution as a result of an antigen-antibody reaction. The amounts of antigens in sample liquid are few, and also when only a small amount of sediment is obtained, the laser nephrometry using dispersion of laser etc. is used suitably. In applying the immunoassay of these each to the measuring method of this invention, setting out of special conditions, actuation, etc. is not needed. What is necessary is to add the usual technical consideration of this contractor to the usual conditions in each approach, and operation information, and just to build the system of measurement of the gene product concerned. About the detail of these general technical means a total theory, a compendium, etc. can be referred to -- [-- for example, inlet ** editing "radioimmunoassay" (Kodansha --) the volume Showa 49 issuance and on inlet ** "** radioimmunoassay" (Kodansha --) The volumes Showa 54 issuance and for Eiji Ishikawa "enzyme immunoassay" (Igaku-Shoin, Showa 53 issuance), The volumes for Eiji Ishikawa "enzyme immunoassay" (the 2nd edition) (Igaku-Shoin, Showa 57 issuance), The volumes for Eiji Ishikawa "enzyme immunoassay" (the 3rd edition) (Igaku-Shoin, Showa 62 issuance), "Methods in Enzymology (Methods in ENZYMOLOGY)" Vol.70 (Immunochemical Techniques (Part A)), The said document Vol.73 (Immunochemical Techniques (Part B)), The said document Vol.74 (Immunochemical Techniques (Part C)), The said document Vol.84 (Immunochemical

Techniques (Part D:Selected Immunoassays)), The said document Vol.92 (Immunochemical Techniques (Part E:Monoclonal Antibodies and General Immunoassay Methods)), The said document Reference], such as Vol.121 (Immunochemical Techniques(Part I:HybridomaTechnology and Monoclonal Antibodies)) (above, Academic Press issuance). As mentioned above, sensibility can improve the gene product concerned a quantum by using the antibody of this invention. Furthermore, the various diseases relevant to the gene product concerned can be diagnosed using the antibody of this invention by carrying out the quantum of the gene product concerned in the living body. That is, since the antibody of this invention can detect the gene product with which the function was solved, it is useful as a diagnostic agent of the disease in which the gene product concerned participates. For example, when the gene product concerned participates in a joint function, it is more specifically useful [the antibody of this invention] as a bone or a diagnostic agent of an articular disease as a joint functional-diagnosis agent. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Moreover, the antibody of this invention can be used in order to detect specifically the gene product concerned which exists in analytes, such as body fluid and an organization. Moreover, it can be used for detection of the gene product concerned which exists in each fractionation at the time of production of the antibody column used in order to refine the gene product concerned, and purification, behavior analysis of the gene product concerned in a tested cell, etc. Furthermore, since the antibody of this invention can adjust the function of the gene product [in the living body] concerned, it is useful [it is low toxicity, and] as a bone or a prevention / therapy agent of an articular disease as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy) of mammalian, for example. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, the antibody of this

invention is applicable to the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer. When using the antibody of this invention as the above-mentioned remedy constituent, it can pharmaceutical-preparation-ize using a stock-in-trade. For example, it can manufacture like the remedy constituent containing the compound which has the above-mentioned joint function acceleration operation or the above-mentioned joint depression operation, and can be used.

[0026] [Antisense nucleic acid] This invention offers the antisense nucleic acid to the gene as which the function was solved using the functional break-through approach of this invention. The antisense polynucleotide (nucleic acid) which can check the duplicate or manifestation of a gene (it is hereafter written as the gene concerned) as which the function was solved was cloned, or the determined gene product is designed based on the base sequence information on DNA which carries out a code, and can be compounded. Such a polynucleotide (nucleic acid) can be hybridized with RNA of the gene concerned, it can check composition or the function of this RNA, or can mind an interaction with the gene product relation RNA concerned, and can adjust and control the gene expression concerned. Out of [in-the-living-body and] a living body, the polynucleotide complementary in the array as which the gene product relation RNA concerned was chosen, and the gene product relation RNA concerned and the polynucleotide which can be hybridized specifically are useful, although the gene expression concerned is adjusted and controlled, and it is useful to the therapy or diagnosis of a disease etc. it has homology in a nucleotide including a gene [vocabulary / "it corresponds"], a base sequence, or the specific array of a nucleic acid -- it is -- it is -- a complementary thing is meant. The finger of the amino acid of the peptide (protein) in the command guided from the array or its phase complement of the nucleotide (nucleic acid) "corresponds" between a nucleotide, a base sequence or a nucleic acid, and a peptide (protein) is usually carried out.

[0027] Although a 5 'edge hairpin loop and 5' edge 6-base pair repeat, 5 'edge untranslation region, polypeptide translation initiation codon, protein coding region, ORF translation initiation codon, and 3' edge untranslation region, and 3 'edge palindrome field and 3' edge hairpin loop of the gene concerned can be chosen as a desirable object domain, any fields in the gene concerned can be chosen as an object. It can be said that the relation with the polynucleotide which can hybridize the relation between the object nucleic acid and a polynucleotide complementary to a part of object domain [at least] with an object is "antisense." The poly deoxy nucleotide in which

the antisense polynucleotide contains the 2-deoxy-D-ribose, The polynucleotide of the type of others which are the poly deoxy nucleotide containing D-ribose, a pudding, or N-glycoside of a pyrimidine base, Or the polymer of others containing the polymer (for example, a commercial protein nucleic acid and a commercial synthetic array specific nucleic-acid polymer) of others which have a non-nucleotide frame, or special association (However, this polymer contains a nucleotide with the arrangement which permits pairing of a base and adhesion of a base which are found out in DNA or RNA) etc. -- it is mentioned. They The double stranded DNA, a single stranded DNA, the 2 chain RNA, single stranded RNA, Furthermore, it can be a DNA:RNA hybrid. Further A non-modified polynucleotide (or non-modified oligonucleotide), That to which still better known qualification was added, for example, a thing with the indicator known for the field concerned, that to which the cap was attached, the methylated thing, and one or more natural nucleotides -- a relative -- what was permuted by the object -- That to which intramolecular nucleotide qualification was carried out, for example, non-electrification association A phospho RUAMI date for example, methyl phosphonate and phospho triester -- A thing with a carbamate etc., association which has a charge, or sulfur content association What (for example, has phosphorothioate, phosphorodithioate, etc.), for example, protein (nuclease, nuclease inhibitor, and toxin --) What has side chain radicals, such as an antibody, transit peptide, poly-L-lysine, etc. and sugar (for example, mono-saccharide etc.), A thing with INTAKARENTO compounds (for example, an acridine, PUSORAREN, etc.), You may have the thing containing chelate compounds (for example, a metal, a metal with radioactivity, boron, the metal of an oxidizing quality, etc.), a thing containing an alkylating agent, and embellished association (for example, nucleic acid of alpha anomer mold etc.). It not only contains a pudding and a pyrimidine base, but what has the heterocycle mold base of others which were embellished may be included with the "nucleoside", the "nucleotide", and the "nucleic acid" here. Such a qualification object may include the heterocycle of the methylated pudding and a pyrimidine, the acylated pudding and a pyrimidine, or others. A part for a sugar part may be embellished again, for example, one or more hydroxyl groups may be permuted by the halogen, the aliphatic series radical, etc., or the embellished nucleotide and the embellished nucleotide may be changed into functional groups, such as the ether and an amine.

[0028] The antisense polynucleotide (nucleic acid) of this invention is RNA, DNA, or the embellished nucleic acid (RNA, DNA). Although the thing of resistance is mentioned to decomposition of the sulfur derivative, thio phosphate derivative and the poly nucleoside amide of a nucleic acid, or an oligo nucleoside amide as an example of the embellished nucleic acid, it is

not limited to it. The antisense nucleic acid of this invention is designed preferably, and is sold at the following policies. That is, supposing toxicity makes bigger compatibility over the sense chain which makes intracellular antisense nucleic acid more stable, which raises the cell permeability of antisense nucleic acid more and which is made into a target, the toxicity of antisense nucleic acid will be made into a smaller thing. in this way, many qualification is got to know in the field concerned -- having -- **** -- for example, -- J.Kawakami et al., Pharm Tech Japan, Vol.8, pp.247, and 1992; Vol.8, pp.395, and 1992; S.T.Crooke et al.ed., Antisense Research and Applications, CRC Press, and 1993 etc. -- there is disclosure. The antisense nucleic acid of this invention is made to change, or may contain the embellished sugar, a base, and association, and a grant is made with liposome and a special gestalt like a microsphere, it is applied by gene therapy, or it may be given with the added gestalt. In this way, an interaction with a poly cation object like the poly lysine which works as what is used with an addition gestalt so that the charge of a phosphoric-acid radical frame may be neutralized, and a cell membrane is raised, or a thing of rough aquosity called lipids (for example, phospholipid, cholesterol, etc.) which make the incorporation of a nucleic acid increase is mentioned. As a desirable lipid, cholesterol and its derivatives (for example, cholesteryl chloro formate, cholic acid, etc.) are mentioned for adding. Such a thing can be made to adhere to 3 'edge or 5' edge of a nucleic acid, and may be made to adhere through a base, sugar, and intramolecular nucleoside association. As other radicals, it is the radical for a cap arranged specifically, and the thing for preventing decomposition by nucleases, such as exonuclease and RNase, is mentioned to 3 'edge or 5' edge of a nucleic acid. Although the protective group of the hydroxyl group known for the fields concerned including glycols, such as a polyethylene glycol and tetraethylene glycol, is mentioned as a radical for such a cap, it is not limited to it.

[0029] The antisense nucleic acid of this invention is low toxicity, and since it can adjust the function of the gene concerned in the living body or a gene product, it is useful as a bone or a prevention / therapy agent of an articular disease as remedy constituents, such as joint function accommodation medicine (preferably articular disease remedy) of mammalian, for example. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned. Furthermore, the antisense nucleic acid of

this invention is applicable to the therapy of gum disease, restoration of the periodontium deficit in a periodontal disease, stabilization of a dental implant, residual-ridge formation, restoration of the uranoschisis, etc. in a dentistry field as an osseous tissue repairing agent after surgical operations, such as a multiple myeloma, lung cancer, and a breast cancer. When using the antisense nucleic acid of this invention as the above-mentioned remedy constituent, after inserting the antisense nucleic acid concerned in suitable independent or vectors, such as a retrovirus vector, an adenovirus vector, and an adenovirus-associated virus vector, it can carry out according to a stock-in-trade. The antisense nucleic acid concerned remains as it is, or can be prescribed for the patient with a catheter like a gene gun or a hydro gel catheter with the adjuvant for acceleration of intake. For example, the antisense nucleic acid concerned can be parenterally used in the form of injections, such as water, an axenic solution with the other liquid which can be permitted pharmacologically, or a suspension agent, in taking orally as the tablet and capsule which gave glycocalyx if needed, elixirs, a microcapsule agent, etc. For example, it can manufacture by mixing with the antisense nucleic acid concerned with the unit dosage gestalt required of the pharmaceutical preparation implementation generally accepted with the well-known support which can be accepted physiologically, a flavor agent, an excipient, a vehicle, antiseptics, the stabilizer, the binder, etc. A dosage with the directed range suitable for the amount of active principles in these pharmaceutical preparation is obtained. As an additive which can mix with a tablet, a capsule, etc., a flavor agent like plumping agents, such as gelatin, corn starch, tragacanth, a binder like gum arabic, an excipient like a crystalline cellulose, corn starch, gelatin, and an alginic acid, lubricant like magnesium stearate, cane sugar, a lactose or a sweetening agent like saccharin, peppermint, a dirt mono-oil, or a cherry etc. is used, for example. When dispensing unit form voice is a capsule, liquefied support still like fats and oils can be contained into the ingredient of the above-mentioned type. The sterile constituent for injection can prescribe natural appearance vegetable oil, such as an active substance in a vehicle like water for injection, sesame oil, and coconut oil, etc. according to the usual pharmaceutical preparation implementation of making it dissolve or suspend etc. As aquosity liquid for injection, the isotonic solutions (for example, D-sorbitol, D-mannitol, a sodium chloride, etc.) containing the adjuvant of a physiological saline, grape sugar, or others etc. are used, for example, and you may use together with a suitable solubilizing agent (an example, ethanol), for example, alcohol, polyalcohol (an example, propylene glycol, polyethylene glycol), a nonionic surfactant (an example, polysorbate 80 TM, HCO-50), etc. As oily liquid, sesame oil, soybean oil, etc. are used and you may use together with benzyl benzoate, benzyl alcohol, etc. which are a solubilizing

agent, for example. Moreover, the above-mentioned remedy constituent may be blended with a buffer (for example, a phosphate buffer, the sodium acetate buffer solution), aponia-ized agents (for example, a benzalkonium chloride, procaine hydrochloride, etc.), stabilizers (for example, a human serum albumin, a polyethylene glycol, etc.), preservatives (for example, benzyl alcohol, a phenol, etc.), an antioxidant, etc. Suitable ampul is usually filled up with the prepared parenteral solution.

[0030] Thus, the remedy constituent obtained is safe, and since it is low toxicity, a medicine can be prescribed for the patient to mammalians (for example, Homo sapiens, Latt, a mouse, a rabbit, a sheep, Buta, a cow, a cat, a dog, an ape, etc.), for example. Although it is different with the object organ for administration, a symptom, a medication method, etc., in internal use, generally in an osteoarthritis patient, about 0.1mg - 100mg per day of about 1.0-50mg of doses of the antisense nucleic acid concerned is about 1.0-20mg more preferably (as 60kg). It is convenient to prescribe [in / for example / usually / in the form of injections / an osteoarthritis patient (as 60kg)] more preferably about about 0.01-30mg [per day] about about 0.1-20mg about about 0.1-10mg for the patient by the intravenous injection, although the 1-time dose changes with the object organ for administration, a symptom, medication methods, etc. when prescribing a medicine for the patient parenterally. The amount which converted into per 60kg also in other animals can be prescribed for the patient. Furthermore, the antisense nucleic acid concerned can also be used as an oligonucleotide probe for a diagnosis for investigating existence of DNA developed using the technique of this invention in an organization or a cell, and its manifestation situation. Furthermore, since the antisense nucleic acid of this invention can detect the gene as which the function was solved, it is useful as a diagnostic agent of the disease in which the gene concerned participates. For example, when the gene concerned participates in a joint function, the antisense nucleic acid of this invention is useful as a bone or a diagnostic agent of an articular disease as a joint functional-diagnosis agent. Metabolic bone diseases, such as non-metabolic bone disease; bone deficits, such as fracture [in / as an example of a bone or an articular disease / an orthopedics field], the refracture, bone deformation / deformation spondylosis, an osteosarcoma, myeloma, osteogenesis imperfecta, and scoliosis, osteoporosis, osteomalacia, rickets, fibrous ostitis, renal rickets, a ****-CHIETTO disease, and a rigidity myelitis; the articular disease represented by chondropathies, such as hypertrophic arthritis and rheumatoid arthritis, is mentioned.

[0031] [Gene-diagnosis agent] the gene (DNA and mRNA) as which the function was solved using the functional break-through approach of the gene of this invention By using it as a probe, for example, Homo sapiens or a homeotherm for example, Latt, a mouse, a guinea pig, a rabbit, Tori, a sheep,

and Buta -- Since the abnormalities of the gene concerned in a cow, a horse, a dog, a cat, an ape, a chimpanzee, etc. (abnormality of the genes), for example, the breakage on the gene concerned, mutation or manifestation lowering, an increment or excess of a manifestation of the gene concerned, etc. is detectable, it is useful also as a gene-diagnosis agent. the above-mentioned gene diagnosis -- for example, the very thing -- it can carry out by well-known Northern hybridization, the PCR-SSCP method, etc. For example, it can be diagnosed that possibility of being diseases, such as an articular disease accompanied by a joint depression, is high when the mutation of the gene concerned is detected by the case where the excess of a manifestation is detected by Northern hybridization, or the PCR-SSCP method.

[0032] [The screening approach of promotor activity accommodation medicine] The screening procedure of a compound which adjusts the promotor activity concerned characterized by for this invention to measure the promotor activity concerned when not prescribing for the patient the case where a trial compound is prescribed for the patient, and a trial compound, in the reporter gene assay approach using the promotor who is controlling the gene expression as which a function or drug effect was solved using the functional break-through approach or the pharmacometrics approach of (1) this invention offers. More specifically, it is the primary cell culture which constitutes a joint, and H9c2. The primary cell culture or H9c2 which constitutes the joint which introduced the gene manufactured using the cell strain or the meniscus syndesmectomy model animal of this invention Reporter gene assay is performed by making a cell strain into a host cell. reporter gene assay -- the very thing -- the approach of a publication can be used in DEBEROPUMENTO, the 124th volume, 793 - 804 pages, 1997, etc. in a well-known approach (J. B.C.), for example, THE Journal of Biological Chemistry, the 272nd volume, 22800 - 22808 pages, and 1997. As a trial compound, a peptide, protein, living body origin nonpeptidic compounds (sugar, lipid, etc.), a synthetic compound, a microorganism culture, a cell extract, a vegetable extract, an animal tissue extract, etc. may be mentioned, and these compounds may be new molecular entities and may be well-known compounds, for example. Culture of the cell which constitutes a joint can be performed like the above. Promotor activity can be measured by investigating the amount of manifestations of a reporter gene. For example, the amount of manifestations of a reporter gene can be measured according to the approach according to approaches, such as Northern blotting, Reverse transcription-polymerase chain reaction (RT-PCR), and TaqMan polymerase chain reaction, or it.

[0033] In this approach, the amount of manifestations of the reporter gene at the time of prescribing a trial compound for the patient can choose 30% or

more preferably on about 20% compared with the case where a trial compound is not prescribed for the patient, as a compound which reinforces the activity of the gene as which the function was solved in the compound reinforced about 50% or more more preferably, or its gene product. The amount of manifestations of the reporter gene at the time of on the other hand prescribing a trial compound for the patient compared with the case where a trial compound is not prescribed for the patient can choose 30% or more preferably on about 20% as a compound which checks the activity of the gene as which the function was solved in the compound checked about 50% or more more preferably, or its gene product. Therefore, the compound which reinforces the activity of the gene as which the function was solved, or its gene product is useful as remedies, such as the gene concerned or a functional enhancement agent of the gene product. The compound which, on the other hand, checks the activity of the gene as which the function was solved, or its gene product is useful as remedies, such as the gene concerned or a functional inhibitor of the gene product. These remedies can be manufactured like the above mentioned remedy constituent, and can be used.

[0034]

[Example] Although an example is given to below and this invention is explained to it still more concretely, this invention is not limited to it.

[0035]

[Example 1] The preparation male Sprague-Dawley rat (9 weeks old : 320 to 370 g weight) of an operation was anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Hind-foot knee region hair of either the right or the left was ****(ed) by hair clipper, and it was put to sleep on the operating table at least to turning up. The operating area was disinfected with the ethanol solution 80%. The sterilized hind-foot knee region skin was cut open in the direction of a culmination, the connective tissue [directly under] of it was exfoliated, and the knee joint was exposed. It is independently cut open in the direction of a culmination from the left right flank of the tendon located in the upper part, and muscles, and it was made to move in the direction of an outside, with the tendon and muscles attached which remained the patella so that the tendon located in a body side direction from the perimeter of a patella may not be cut. The knee joint was bent after migration of a patella, the boundary section of a femur and a tibia was cut open from the transverse plane, and the tendon and muscles which are located in the boundary section of a femur and a tibia were cut open in the direction of the inside in the shape of a circle, warning against damaging a joint following this incision section.

[0036]

[Example 2] While cutting it open in the direction of the cutting inside of a

tibial collateral ligament, an anterior cruciate ligament, and a posterior cruciate ligament, it runs against a tibial collateral ligament. The tibial collateral ligament was cut warning against damaging the facies articularis. In order to carry out opening of the cavum articulare furthermore, the boundary section of a femur and a tibia was cut open to knee back. Next, having inserted ophthalmology BASAMI from the knee-joint transverse plane, and extending the cavum articulare, the anterior cruciate ligament and posterior cruciate ligament which connect a femur and a tibia were checked, and were cut in order. It warns to damage and twist the blood vessel of branching of the thigh condition pulse which exists around a joint at this time.

[0037]

[Example 3] It becomes possible by cutting three ligaments, a tibial collateral ligament, an anterior cruciate ligament, and a posterior cruciate ligament, in the excision example 2 of medial meniscus to carry out opening of the knee joint greatly to outside back. Opening of the knee joint was greatly carried out to outside back, and it checked that the meniscus had combined with the tibia side in connective tissue. The inside side of a meniscus was excised in ophthalmology BASAMI. Although the meniscus is formed in bilateral symmetry from the center of the joint section, this excision is limited only to an inside meniscus from a part for a core. Therefore, an outside meniscus will remain in the tibia juxtaposition facies articularis in the condition of having been tied to connective tissue.

[0038]

[Example 4] After excising closeout and the suture meniscus of a knee joint, the joint was closed so that a femur and a tibia might become the same physical relationship as operation before, and the skin was sutured in order to muscles, connective tissue, and a pan, warning against spoiling the movability of a joint part.

[0039]

[Example 5] The meniscus syndesmectomy model rat manufactured in the pharmacometrics example 4 is used. Artz which is a known over-the-counter medicine object (joint function improvement medicine containing an ARTZ; hyaluronate sodium component; Seikagaku), And a knee joint is medicated with Ro-32-3555 (compound;Arthritis Rheum reported to be effective in the therapy of the osteoarthritis, 1998 Sep;41 1639-44). The curative effect over the osteoarthritis of drugs was confirmed and it checked that the animal model which created by the manufacturing method of this invention could use it for pharmacometrics. The meniscus of right-hand side **** of the 9-weeks old male Sprague-Dawley rat purchased from the Japanese CHARU sliver company was excised. the right-hand side where the drug excised the meniscus -- a leg -- the cavum articulare was medicated. Artz used the pharmaceutical preparation dissolved [10mg //ml]. Moreover, Ro-32-3555

set the last drugs concentration to 20nmol(s) after dissolving in DMSO and ethanol, and used it in the condition of having fully mixed with Artz (10mg/(ml)). The medication method prescribed 100microper each joint I for the patient per week for 2 times and two weeks each time. administration drugs -- business -- the time -- having prepared . Bleeding fatality of Latt was carried out under anesthesia after the administration termination for two weeks, and the knee joint was extracted. The knee joint was fixed at 4 degrees C by the paraformaldehyde 4% overnight. The knee joint was delimed for the knee-joint organization for two weeks with deliming liquid B (Wako Pure Chem) after water washing. next, a law -- paraffin embedding was performed according to the method (a histology approach, Sano **** Nanzando, 1985). Thin sectioning of the produced paraffin block was carried out to the thickness of 5 micrometers with the microtome. Hot bath expansion was carried out, and the after [thin sectioning] intercept was mounted on the slide glass, and was enough dried with 37-degree-C dryer. the produced intercept — after deparaffinization and a law -- according to the method, it enclosed by performing a hematoxylin eosin stain and safranin O dyeing (a histology approach, Sano **** Nanzando, 1985). The joint part histologically medicated with drugs in light field was observed, and it compared with the control group. The cavum articulare was held although joint destruction was not controlled by the Artz administration group as a result of microscope observation. Moreover, by the group which carried out concomitant use administration of Artz and Ro-32-3555, destruction of an articular cartilage was controlled over articular cartilage ******, and the cavum articulare was held. It was shown that the meniscus syndesmectomy model nonhuman mammal which the manufacturing method of this invention manufactures efficiently joint animals used in disease modeling, such as osteoarthritis, and is obtained from the above thing by the manufacturing method of this invention can be used for the functional break-through approach of a gene that the function is not known, the screening approach of a remedy candidate compound, the pharmacometrics approach, etc.

[0040]

[Effect of the Invention] The manufacturing method of the meniscus syndesmectomy model nonhuman mammal of this invention can manufacture efficiently joint animals used in disease modeling, such as osteoarthritis. The meniscus syndesmectomy model nonhuman mammal obtained by the manufacturing method of this invention can be used for the functional break-through approach of a gene that the function is not known, the screening approach of a remedy candidate compound, the pharmacometrics approach, etc.

[Translation done.]